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Mark K. Johnson
P.O. Box 510644
New Berlin, WI 53151-0644

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,791	WOLFF ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *November 17, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed February 8, 2001, is a continuation in part of application 09/312,351, filed May 14, 1999.

Applicants' amendment filed November 17, 2003, has been received and entered. The specification has been amended. Claims 1 and 13 have been amended. Claims 1-13 are pending.

Election/Restriction

As noted in the previous office action, upon reconsideration Groups I and II had been rejoined, and Applicants election of Group I, claims 1-6 and 13 (which now has been rejoined with group II),. Claims 7-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15. Claims 1-6 and 13 are currently under examination as they are drawn to a compound for inserting into an organism comprising (a) a disulfide bond which is cleaved more rapidly that oxidized glutathione and which one of the constituent thiols has a lower pKa than glutathione and (b) a transduction signal wherein the signal is a polymer containing a cationic charge.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

This application contains claims drawn to an invention nonelected with traverse in Paper No. 15. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

The information disclosure statement and references filed November 17, 2003, have been reviewed. A signed copy of the IDS is provided with this action.

It is noted that both the cited references qualify as 102(e) type references, and that each teach disulfide containing compounds containing transduction signals/peptides for the delivery of polynucleotides to a cell. However, the specifications of each do not provide sufficient disclosure or guidance to determine if any of the compounds generated would meet the limitations set forth in claim 1 for the properties of the disulfide bond.

Priority

In traverse of a 102(e) rejection Applicants argue that the instant application has a priority date of May 16, 1998. Currently the only claim for priority in the instant application is as a continuation in part of 09/312,351, filed May 14, 1999 (see first line of specification.). Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 119(e) as follows:

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/085,764, filed May 16, 1998. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet

(37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the

claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Claim Objections

Claim 6 is objected to because of the following informalities: Claim 6 recites the "compound of claim 5 claim 1 wherein the transduction signal..." and there is no conjunction relating between claim 5 and claim 1. There is sufficient antecedent basis in both claims 5 and 1, and is suggested to amend the claim to clearly indicate the claims in the alternative inserting "or", alternatively, making the claim dependent on only one of the claims consistent with claims 2-5.

Appropriate correction is required.

Specification

The amendments to the specification has obviated the basis of the objection and the nucleotide sequence disclosure contained in this application now complies with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". It is noted that the claim has been amended to recite "labile under mammalian [intracellular] physiological conditions" however this is considered new matter.

Applicants argue that the amendment to the claim has obviated the basis of the rejection and pointing to several passages in the specification for the intended use of the claimed compound, and argue that it is the Applicants' opinion that mammalian physiological conditions are well established in the art. See Applicants amendment, page 4, first three paragraphs. Applicants' arguments have been fully considered, but not found persuasive.

Specifically, Applicants have not pointed to any portion of the specification for the literal or specific support of this new amendment. Again, upon review of the specification Examiner can not find literal support for the recitation nor figurative support teaching the metes and bounds encompassed by this embodiment. There are many different mammals in the world, and many different conditions which they require and present themselves as physiological circumstances. Moreover, there a many types of physiological conditions with a single mammal, for example the physiological conditions that exist in the intestine versus the brain or the liver or in a blood vessel, and many physiological conditions that exist even within a cell, such as conditions in the nucleus, cytoplasm, and organelles such as the lysozome or

mitochondria. It is acknowledged that the intended use of the instantly claimed compounds is for the delivery to "a living cell" as set forth by Applicants, however, while it would be conceded that a particular physiological condition could be assessed in a specific cell or maybe in a particular mammalian organ, the limitation of "mammalian physiological conditions" does not provide a clear nor adequate definition of the metes and bounds of all the conditions that may exist in nature. Further, because the physiological conditions are so wide and varied, it fails to adequately describe the nature of the disulfide bond encompassed by the claim. Additionally, the metes and bounds of any specific disulfide bond would be subject to change depending on the physiological condition one were to use to assess the nature of the bond. For example, the conditions for delivery to a living cell in the stomach would be significantly different from the physiological conditions existing in the brain. Moreover, even in these types of examples, the physiological conditions are subject to change depending on the state of the mammal such as before and after eating in the stomach, or normal and hypoxic conditions such those found in a stroke victim.

As stated in the previous office action, to the extent that the claimed compositions and/or methods are not described in the instant disclosure, claim 1 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure". In the instant case, the portions pointed to in the specification by Applicants only provide examples of specific circumstances in which the claimed compounds would or could be used. However, none of these examples provide any guidance to what are the physiological conditions in each circumstance, or how they represent in general the breadth of physiological conditions encompassed by the claims or contemplated as part of the physical limitations of the compound instantly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, newly amended claim 1 is indefinite in the recitation of "mammalian physiological conditions". The specification provides no specific definition of the

conditions encompassed by this term nor methods and guidance for determining what these conditions encompass. It is noted that the specification supports the intended use of the compound in a mammal, however it fails to provide support for what physiological conditions exist in a mammal. Further, since physiological conditions can vary widely within even a single mammal, for example between cells in the stomach and the brain, the claim is indefinite because it is dependent on the physiological condition one chooses to use in determining the metes and bounds of the claim. Dependent claims 2-6 and 13 are included in the basis of the rejection because they fail to further clarify the nature of the physiological condition and only further define the compounds attached to the product.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 5 and 6 stand rejected under 35 U.S.C. 102(a) as being anticipated by Bulaj *et al.* (IDS reference) as evidenced by Szajewski *et al.* (IDS reference).

Claims 1 and 5 stand rejected under 35 U.S.C. 102(b) as being anticipated by Keire *et al.* (IDS reference).

Applicants summarize the basis of the rejection and argue that even though the references teach compounds that meet the physical limitations of the claims, the types of peptides used by Bulaj *et al.* and Keire *et al.* are not transduction peptides. Using the analogy that all squares are rectangles, but not all rectangles are squares Applicants argue that the charge of a peptide alone is not sufficient to make the peptide a transduction signal pointing the teachings of Wender et al (PNAS97(24):13003-13008, 2000) in support of their arguments (bottom of page 4). Summarizing the teach of both Bulaj *et al.* and Keire *et al.* in greater detail, Applicants argue that the teachings of Bulaj *et al.* and Keire *et al.* details how compounds affect the kinetics of a disulfide bond, and fails to teach the use of such compounds for insertion into a mammal (page 5). See Applicants' amendment, bridging pages 4-5. Applicants' arguments have been fully considered, but not found persuasive.

Examiner acknowledges that neither Bulaj *et al.* and Keire *et al.* specifically teach to administer their compounds to a mammal, however the reference is not relied upon as a showing any intended use. This is because the claim recitation "for inserting into a mammal" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). There is nothing in the specific limitations of the claims nor in the teachings of the specification that breath any life into this preamble. Even though the

compound is to be administered to a mammal, the administration comprises any intended use and outcome, thus the compound can even be toxic to the mammal as generally supported by the instant specification of the use of the compound to deliver a toxin. Applicants' arguments that Bulaj *et al.* and Keire *et al.* do not teach to use their compounds for the same use as disclosed in the instant specification is not found persuasive because the intended use of the compound is not limited by any of the required physical characteristics of the compound set forth in the claim (nor generally provided in the teachings of the specification).

With respect to Applicants' arguments that the cationic peptides taught in Bulaj *et al.* and Keire *et al.* are not transduction signals, Examiner acknowledges and accepts Applicants' analogy. Further, as set forth in the previous office action it has been acknowledged that the specification teaches that transduction signal as signals which transport themselves and attached molecules across membranes (page 25, lines 29-30). However, the only guidance and description provided by the instant specification for a transduction signal is the teaching that among peptides there is no specific motif or homology other than that they possess a cationic charge (page 26, lines 1-10). Given this limited guidance in the specification, clearly the peptides taught by Bulaj *et al.* and Keire *et al.* would meet these physical limitations. With respect to Applicants analogy, it was set forth in the previous office action that where the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the present specification has not provided the means nor adequate description to

discern between squares and rectangles. With respect to the teaching of Wender *et al.* it appears that the cited statement pertains specifically to modified forms of the Tat protein. However, more importantly, the citation and the specification in general does not teach that charge alone will not work, only that other types of sequences may be important for more efficient uptake of such peptides. To the contrary the final portion of the citation only indicates that the cationic amino acids 'are less effective' in cellular transport not that they would not work. Clearly the teaching of Wender *et al.* provides further support that cationic peptides from various sources synthetic and natural provide the ability to serve as transduction peptides. Examiner would agree consistent with the results presented in Wender *et al.*, that the ability of a specific peptide sequence to serve as transduction peptide may vary widely, however the efficiency of a peptide or as more broadly set forth in claim 1, 'a transduction signal' is not specifically set forth and not materially to the compound as instantly claimed. Applicants' arguments are not found persuasive because the compounds taught by Bulaj *et al.* and Keire *et al.* anticipate the physical limitations set forth in the claims in light of the teachings of the present specification. Further, the evidence of record clearly demonstrates that cationic peptides from various sources serve as transduction peptides, albeit some sequences provide better and some provide worse efficiencies in cellular uptake.

As set forth in the previous office action, Bulaj *et al.* teach two disulfide linked peptides, Pti38 and Pti51a. Each peptide contains positive charges and have a lower pKa as a consequence (see page 8968, top of second column). The specific pKa is 8.26 for Pti38 and 8.38 for Pti51a (page 8967, Table 1). Szajewski *et al.* teach that the pKa of glutathione is 8.72 (see page 8965, bottom of second column equation 4). Each peptide has a positive charge and is linked to a disulfide containing compound with a pKa lower that glutathione, the compounds Pti38 and Pti51a anticipate the claims because they meet the structural limitations required by the claims.

With respect to Keire *et al.*, three disulfide containing compounds with a pKa lower than glutathione are taught. Each compounds contains primary amines which are capable of being positively charged (see page 126, Table IV) and thus, can serve as transduction signal. Since, in each case each compound contains a positive charge and is linked to a disulfide containing compound with a pKa lower that glutathione, the compounds taught by Bulaj *et al.* and Keire *et al.* anticipate the claims because they meet the structural limitations required by the claims.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 1, 2, 5, 6 and 13 stand rejected under 35 U.S.C. 102(e) as being anticipated by Stein *et al.* (6,258,774 B1).

Applicants summarize the basis of the rejection and argue that the actual compound delivered to a cell would not meet the limitations of the claims as being cleaved more rapidly that oxidized glutathione (page 5). Further, Applicants argue that the disclosure of Stein *et al.* teach away from the instant invention because they teach modulation of a compound to make it more stable, and released more slowly from the carrier (page 6). See Applicants amendment, pages 5-6. Applicants' arguments have been fully considered, but not found persuasive.

Initially, upon review of the teachings of Stein *et al.* for the conjugate of Tat to the disulfide compound, Examiner agrees that there is no evidence that once such a compound is formed, that it would meet the physical limitation of (a) being more rapidly cleaved that oxidized glutathione as set forth in the instant claims. While the proposed mechanism for reduction of such a disulfide bond in the cytosol of a cell is by glutathione there is no teaching to the rate of reduction as compared to oxidized glutathione, or methods of generating compound with any

specific rate of cleavage. Further, Examiner would agree that the general guidance provided by Stein *et al.* is for the generation of disulfide bond containing compounds that are more stable by affecting the steric hindrance to the bond, though it is noted that an artisan would readily recognize that affects and conditions that make such a compound less stable, but again there is no specific teaching to generate any specific rate of cleavage relative to glutathione. However, Stein *et al.* teach materials and conditions that satisfy (b) a disulfide bond constructed from thiols in which one of the constituent thiols has a lower pKa than glutathione. In this case the starting material shown in figure 1 has a physical characteristic that has a lower pKa than glutathione, thus serves to anticipates (b) as constituent having a lower pKa than glutathione used to construct the disulfide bond of the claimed compound. Moreover, the starting material by itself serves to anticipate the claims because it satisfies both the limitations of (a) and (b). As argued above, the recitation "for inserting into a mammal" has not been given patentable weight because the recitation occurs in the preamble. Again, the preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In this case there is nothing in the specific limitations of the claims nor in the teachings of the specification that breath any life into this preamble. Examiner acknowledges that the starting material as exemplified in figure 1 is not administered to a cell, however it meets each of the physical limitation set forth in claims 1, 5 and 6, and thus anticipates the claims. Further, it is acknowledged that the specific examples of compounds made and administered to a cell that

contain Tat as taught by Stein *et al.* do not satisfy the limitation of (a), however they satisfy the limitation of (b) by being generated using a disulfide compound wherein a constituent thiol has a lower pKa than glutathione.

Finally, Applicants argue that the Tat protein used by Stein *et al.* is not the same as disclosed in the instant specification and thus not a transduction signal (page 6). Applicants acknowledge that Stein *et al.* teach a cell uptake promoter however argue that this is not equivalent to a transduction signal. Pointing to the specific examples provided by Stein *et al.*, Applicants argue that the examples are for targeting and when used provide a different mechanism for transportation than do transduction signals (page 6). Applicants arguments are not found persuasive because the instant specification broadly defines a transduction signal functionally as being able to 'transport themselves and attached molecules across membranes" (page 25, lines 29-30). This definition does not exclude various mechanisms, such as endocytosis, for transporting a compound across a membrane of a cell. With respect to the Tat peptide taught by Stein *et al.* and the specific example of a peptide derived from tat provided in the instant specification (page 26, lines 3-4), Examiner acknowledges that the sequences are not the same. However, claim 2 does not specifically set forth or claim the sequence disclosed in the instant specification. The claim has been interpreted as it is directed to a peptide termed tat. In the instant case, the tat peptide (and the tat sequences derived therefrom) taught by Stein *et al.* (column 3, lines 35-65 and SEQ ID Nos: 1-8) contains cationic amino acids, thus meets the physical requirements of a transduction signal as taught in the instant specification.

As set forth in the previous office action, Stein *et al.* teach a disulfide containing conjugate for the delivery of therapeutic agents. More specifically, Stein *et al.* teach that

nucleotide analogs can be attached as therapeutic agents to a disulfide bond (column 2, lines 40-51) and discuss the use of a HIV tat protein (column 2, lines 52-65). Further, Stein *et al.* teach that numerous cell uptake promoters are known and can be conjugated to 'enhance the ability of the carrier and the therapeutic agent to cross a cell membrane' (column 6, lines 47-49). It is noted that Stein *et al.* provide general guidance for the use of disulfide bonds and do not provide specific teaching for the use of disulfide bonds which are cleaved more rapidly than or have a lower pKa than glutathione, however the specific disulfide cross-linkers used in the examples represent disulfide bonds which meet these limitations (see figure 1-starting compounds and third and final products in reaction scheme). Since, Stein *et al.* teach using a tat protein and nucleic acids as therapeutic agents linked to a disulfide containing compound which by example include disulfides with a pKa lower that glutathione, the compounds taught by Stein *et al.* anticipate the claims because they meet the structural limitations required by the claims. Again, where the claimed and prior art products are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 1, 5, 6 and 13 stand rejected under 35 U.S.C. 102(e) as being anticipated by Monahan *et al.* (6,429,200B1).

Applicants note the priority date for Monahan *et al.* as July 17, 1998, and that the instant application has the priority date of May 16, 1998. Thus, Monahan *et al.* does not qualify as prior art. See Applicants' amendment, bottom of page 6. Applicants' arguments have been fully considered but not found persuasive.

As noted above in the section regarding priority, the instant application only claims benefit to 09/312,351 which was filed May 14,1999. Therefore, Monahan *et al.* qualifies as a 102(e) type reference. Examiner would agree that if the priority claim were made to the provisional application that 09/312,351 claims benefit, **and** there is adequate support for the claimed invention in the priority documents, the claim for priority could be perfected obviating the use of the Monahan *et al.* reference as a 102(e) type reference.

As noted in the previous office action, the instant application and US Patent 6,429,200B1 have some common inventors, however the complete inventive entity listed is not the same. The instant application has Rozema and '200 has Hagstrom listed as inventors. Because the instant application and the '200 patent differ by two different inventors the teaching of '200 is being considered to be by another. US Patent '200 provides the same general guidance for the chemical linkage of conjugates through disulfide bonds recited in the instant claims (see for example column 8, lines 5-28). Further, '200 contemplates conjugating gene transfer enhancing agents (column 11, lines 14-21) such as compounds and peptides which aid in the uptake of the compound conjugates. Finally, '200 teaches that a polynucleotide can be attached to the complex for delivery to a cell (column 12, lines 43-48). Additionally, it is noted that the

claims of '200 encompass the instant claims specifically reciting that the complex comprise a enhancing ligand (claim 6) and that it contains a disulfide bond (claim 8). Since the only specific reference in '200 to a disulfide bond is exactly the same as instantly claimed, the nature of the disulfide bond set forth in claim 8 is being interpreted in light of this teaching.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 1-6 and 13 stand rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Applicants do not specifically address the basis of the 102(f) rejection in the instant amendment, therefore the rejection is maintained for the reasons of record. As set forth in the previous office action, US Patent 6,429,200 B1 provides the same general guidance for the chemical linkage of conjugates through disulfide bonds set forth in the instant claims (see for example column 8, lines 5-28). Further, '200 contemplates conjugating gene transfer enhancing agents (column 11, lines 14-21) such as compounds and peptides which aid in the uptake of the compound conjugates. In dependent claim 8 specifically recites that the claimed complexes and process of using contain a disulfide bond (column 24). Upon review of the specification the only teaching for any specific form of a disulfide bond is found at column 8, lines 5-28, which is the same as instantly claimed. Upon review both the instant application and '200 have claims encompassing products containing disulfide bonds and methods of use which are the same. It is not clear why the inventors on each of the patent and the application are not the same.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

Joe Woitach
AU1632